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NEPHROLOGY FORUM

Renal osteodystrophy

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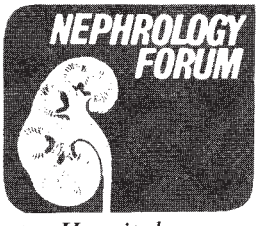
The *Nephrology Forum* is designed to relate the principles of basic science to clinical problems in nephrology.



Case presentation

A 66-year-old man with chronic renal failure was admitted to the Wadsworth VA Medical Center for evaluation of bone pain and severe muscle weakness. Approximately 3 years prior to admission, an elevated serum creatinine of 6 mg/dl was first detected. Evaluation at that time included an intravenous pyelogram, which revealed bilateral scarred and shrunken kidneys without evidence of obstruction. The 24-hour urine protein excretion was 1.5 grams; serum calcium, 8.6 mg/dl; serum phosphorus, 6.5 mg/dl; and alkaline phosphatase, 90 IU. One urine culture was sterile and the anti-nuclear antibody was negative.

Renal failure progressed and 18 months prior to admission the patient was started on maintenance hemodialysis. He did well on dialysis except for the development of bone pain and severe muscle weakness.

Medications at the time of admission included: digoxin, 0.125 mg every other day; Dilantin®, 300 mg daily; aluminum hydroxide, 3 tabs three times daily. Physical examination revealed: blood pressure 140/70; pulse 80/min; respiration, 12/min; temperature, 37.5° C. A grade I/VI systolic murmur was heard at the left sternal border. A functioning arteriovenous fistula was present in the right arm. The remainder of the physical examination was unremarkable. Laboratory data revealed the following: hematocrit, 34%; WBC, 7500/mm^3; BUN, 85 mg/dl; creatinine, 10.7 mg/dl; serum calcium, 10.2 mg/dl; and serum phosphorus, 3.6 mg/dl. The serum magnesium was 2.9 mEq; serum sodium, 138 mEq; serum potassium, 5.4 mEq; serum chloride, 97 mEq; and serum bicarbonate 18 mEq per liter. The alkaline phosphatase was 217 units; serum albumin, 3.8 g/dl; total protein 8 g/dl; serum immunoreactive parathyroid hormone (iPTH), 1.55 ng/ml (normal less than 0.4 ng/ml); and 25-hydroxycholecalciferol, 19 ng/ml (normal = 12–60 ng/ml). Roentgenograms revealed subperiosteal resorption of both hands and distal clavicles. One day after admission, an ileal crest bone biopsy was performed.

The biopsy showed increased resorbing and forming surface, increased osteoid (18.3% unmineralized bone), and severe marrow-space fibrosis (4.8%) (Fig. 1). These findings were interpreted as consistent with osteomalacia and osteitis fibrosa with osteitis fibrosis predominating.

Treatment with 1,25-dihydroxycholecalciferol [1,25$(OH)_2D_3$] was initiated at a dose of 1 μg/day, and aluminum hydroxide was continued at a dose of 3 tabs three times daily. Within one month of initiation of treatment, the patient's muscle weakness improved dramatically and his bone pain diminished. By two months, when the serum calcium was 10.0 mg/dl and the serum phosphorus was 3.0 mg/dl, the alkaline phosphatase had declined slightly to 180 units and the PTH had fallen to 0.95 ng/ml. By 6 months, the serum alkaline phosphatase had fallen further to 105 units, serum calcium was then 12 mg/dl, and serum phosphorus was 7 mg/dl. The serum calcium continued to rise to 13.2 mg/dl and the 1,25$(OH)_2D_3$ was discontinued. One month later a repeat bone biopsy was performed. Serum calcium at the time of biopsy was 10.4 mg/dl; serum phosphorus, 4.4 mg/dl; alkaline phosphatase, 95 units; and serum PTH 0.22 ng/ml. The patient's clinical course is shown in Fig. 2.

The repeat biopsy showed an increase in the forming surface, a slight decrease in the resorbing surface, and a marked reduction in marrow-space fibrosis (1%) (Fig. 3). Percentage mineralization had improved to 95.1%.

Discussion

DR. JACK W. COBURN *(Chief, Nephrology Section, VA Wadsworth Medical Center, and Professor of Medicine, UCLA School of Medicine, Los Angeles, California):* This patient presents a number of features characteristic of symptomatic renal osteodystrophy. I will use this term in a broad, generic sense to include all skeletal abnormalities in uremia, i.e., osteitis fibrosa, osteomalacia, osteosclerosis, and growth failure in children. On the basis of the radiographic findings of increased subperiosteal resorption and elevated levels of serum immunoreactive parathyroid hormone (iPTH),

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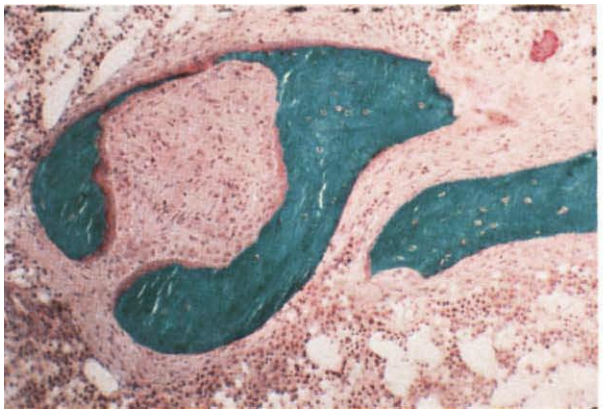

Fig. 1. *Pretreatment bone biopsy showing extensive marrow fibrosis.* There is an increase in unmineralized osteoid (dark red) underlying rows of osteoblasts. (The mineralized bone is blue.) Goldner's modification of Masson's trichrome stain. (Photomicrograph supplied courtesy of Dr. Donald Sherrard, VA Hospital, Seattle, Washington.)

Fig. 3. *Biopsy obtained after 9 months of treatment with 1,25(OH)$_2$D$_3$, 1.0 μg/day.* There is a marked reduction in marrow fibrosis and improvement in mineralization, although an increase in unmineralized osteoid persists. Goldner's modification of Masson's trichrome stain. (Photomicrograph supplied courtesy of Dr. Donald J. Sherrard, VA Hospital, Seattle, Washington.)

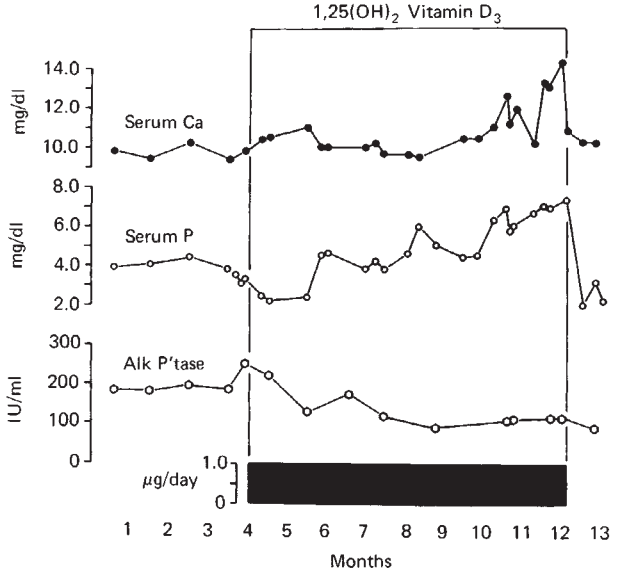

Fig. 2. *Serial levels of serum calcium, phosphorus, and alkaline phosphatase during treatment with 1,25(OH)$_2$D$_3$.* The early fall in serum phosphorus level and the later rise in both serum calcium and phosphorus are apparent. The latter events occurred after alkaline phosphatase had fallen toward normal. The prompt decreases in both serum calcium and phosphorus following the withdrawal of 1,25(OH)$_2$D$_3$ are evident. (Reproduced from Reference 74, courtesy of Dr. W. de Gruyter.)

there is little doubt that our patient has significant secondary hyperparathyroidism.

Pathogenesis of secondary hyperparathyroidism

Before discussing the clinical features of this patient, I will review the factors thought to produce secondary hyperparathyroidism in uremia. These pathogenetic factors, believed to originate early in the course of renal disease, presumably are operative for many years before the patient manifests overt bone disease in the late stages of advanced renal insufficiency [1]. A decrease in ionized calcium in the blood is probably the only important factor that increases the secretion of parathyroid hormone (PTH) and leads to the consequent parathyroid hyperplasia. Major factors leading to hypocalcemia in renal failure include phosphate retention, abnormalities of vitamin D metabolism, and a reduced skeletal response to the calcemic action of PTH. Other conditions, listed in Table 1, also might be contributory.

Phosphate retention. Slatopolsky et al have suggested that transient and even undetectable increments in serum phosphorus levels occur as GFR decreases early in the course of renal failure [2]. They argued that such transient hyperphosphatemia lowers blood calcium and increases PTH secretion, which in turn reduces the tubular reabsorption of phosphate and leads to phosphaturia. Thus, serum phosphorus and calcium levels return toward normal, but only at the expense of inducing a higher circulating level of PTH. Considerable evidence, primarily derived from studies in dogs with reduced renal function, supports the view that phosphate retention plays a primary role in the pathogenesis of secondary hyperparathyroidism in renal failure [3, 4, 5]. A notable problem with this theory is that such increments in serum phosphorus levels have

not been identified, and, in fact, serum phosphorus levels are often low or normal in patients with mild renal insufficiency [6, 7]. When renal function falls below 25% of normal, overt hyperphosphatemia frequently develops, and this elevation of serum phosphorus clearly can be an important factor in the development of secondary hyperparathyroidism at this stage of renal failure [8].

Abnormalities of vitamin D metabolism. Strong evidence indicates that disorders in vitamin D metabolism alter the regulation of calcium and phosphorus in uremic patients [9]. It is now apparent that vitamin D itself, although largely inactive, is a precursor of more active sterols. Thus, either endogenous or exogenous vitamin D_3 first is converted in the liver to 25-hydroxy-vitamin D_3 [10], the major circulating form of vitamin D [11]. This sterol then undergoes 1-hydroxylation in the cortex of the kidney [12] to form 1,25-dihydroxy-vitamin D_3[$1,25(OH)_2D_3$]. The latter sterol provides a more potent stimulus to intestinal calcium absorption than do any of the other forms of the vitamin [13].

The renal generation of $1,25(OH)_2D_3$ is subject to physiologic regulation: it is stimulated by a diet low in calcium [14], increased levels of PTH [15, 16], and hypophosphatemia [17]. It can be inhibited by a high-calcium diet, hyperphosphatemia [17], and $1,25(OH)_2D_3$ itself [18]. Given the central regulatory role of the kidney in calcium and phosphorus metabolism, it is not surprising that vitamin D metabolism is altered in patients with renal insufficiency.

Table 1. Conditions that might contribute to altered calcium homeostasis and bone disease in renal failure[a]

A.	Hypocalcemia and secondary hyperparathyroidism
	1. Retention of phosphate
	2. Altered bioactivation of vitamin D
	3. Skeletal resistance to PTH
	4. Reduced degradation of PTH
B.	Defective mineralization of bone
	1. Abnormal collagen synthesis (possibly related to vitamin D)
	2. Abnormal crystal growth and maturation
	3. Accumulation of pyrophosphate and/or magnesium in bone
	4. Reduced carbonate content of bone
C.	Factors of variable and uncertain role
	1. Heparin administration
	2. Acidosis
	3. Phosphate deficiency
	4. Vitamin D loss with nephrotic syndrome
	5. Skeletal accumulation of trace elements (e.g., fluoride, aluminum)
	6. Modification by treatment
	a. Anticonvulsants, other drugs
	b. Parathyroidectomy
	c. Vitamin D
	d. Dialysate Ca, Mg, etc.

[a] Adapted from Ref. 91.

When does this abnormality of vitamin D metabolism develop during the course of progressive renal insufficiency? A decrease in the generation of $1,25(OH)_2D_3$ early in the course of the disease could lead to both decreased calcium absorption and decreased action of PTH on the bone, processes that in turn would lead to hypocalcemia. Hypocalcemia would stimulate PTH secretion, which would be expected to increase the renal generation of $1,25(OH)_2D_3$ and to restore serum levels of $1,25(OH)_2D$, intestinal calcium absorption, and serum calcium to normal; all of these changes would occur at the expense of an increased level of serum PTH. The data bearing on the question are not conclusive; however, the intestinal absorption of calcium is normal in most patients with mild to moderate renal insufficiency [7, 19]. Preliminary studies of blood levels of serum $1,25(OH)_2D$ in patients with early renal insufficiency have yielded conflicting results. Slatopolsky et al reported normal or slightly increased levels of $1,25(OH)_2D$ in adults with creatinine clearances above 30 ml/min [20], whereas Portale et al found reduced levels in children with an average GFR of 41 ml/min [21]. It is possible that high PTH levels maintain the serum levels of $1,25(OH)_2D$ near normal in azotemic patients until renal insufficiency becomes marked. The mechanism of reduced renal generation of $1,25(OH)_2D_3$ in patients with mild to moderate renal insufficiency is uncertain; phosphate retention and diminished tubular reabsorption of phosphate, both of which occur early in the course of renal insufficiency, could reduce the generation of $1,25(OH)_2D_3$ for any given level of PTH secretion. Preliminary data of Llach et al suggest that in patients with mild renal insufficiency, dietary phosphate restriction in proportion to the degree of reduction in GFR is associated with an increase in intestinal calcium absorption and a fall in serum iPTH [22].

Although we are still uncertain whether vitamin D metabolism is altered early in the course of renal insufficiency, most data indicate that the blood levels of $1,25(OH)_2D_3$ are low or undetectable in end-stage uremia [23, 24]. In advanced renal disease, the lack of $1,25(OH)_2D_3$ probably contributes importantly to the reduced intestinal absorption of both calcium and phosphorus, the impaired calcemic response to PTH, and retarded growth in children. Moreover, many of these abnormalities can be restored to normal after treatment with doses of

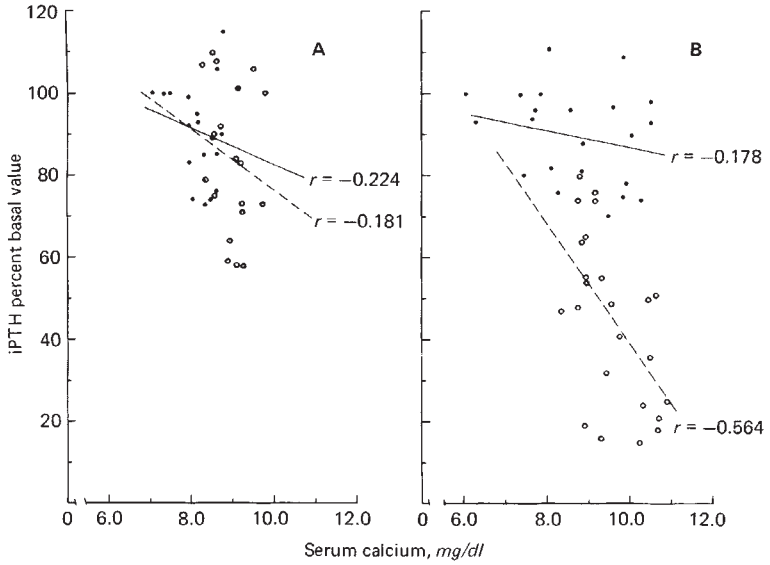

Fig. 4. *Correlation between serum iPTH and serum calcium concentrations during the slow intravenous calcium infusion in ricketic puppies.* The animals were injected with either vehicle alone (A) or 1 μg of $1,25(OH)_2D_3$ (B) 4 hours before the initiation of calcium infusion. Samples collected during the initial 90 minutes of infusion, shown as solid circles, have a continuous regression line, whereas samples obtained between 90 minutes and 180–200 minutes of the calcium infusion are shown by open circles and an interrupted line. (Reproduced from Ref. 34 with the permission of The Endocrine Society.)

$1,25(OH)_2D_3$ that are presumably in the physiologic range [25–29].

Deficiency of $1,25(OH)_2D_3$ also could lead to secondary hyperparathyroidism by virtue of a direct effect of this sterol on the parathyroid gland. Brumbaugh et al have described specific cytoplasmic receptors, similar to those found in known target tissues for vitamin D_3, for $1,25(OH)_2D_3$ in the parathyroid glands [30]. Moreover, certain data suggest that $1,25(OH)_2D_3$ can directly inhibit PTH secretion [31], although such data have not invariably been confirmed [32, 33]. Oldham et al suggested that $1,25(OH)_2D_3$ might modulate PTH secretion at any given level of blood calcium; data supporting this view appear in Fig. 4 [34]. In the absence of $1,25(OH)_2D_3$, a higher level of serum calcium might be needed to produce a similar degree of suppression of PTH secretion. At this point, such a suggestion is speculative and further studies are needed to clarify this possible action of vitamin D.

Despite the low levels of $1,25(OH)_2D_3$ found in patients with advanced renal failure, many uremic patients lack features of vitamin D deficiency. Intestinal calcium absorption is not uniformly reduced [7, 35] and osteomalacia occurs in only a small fraction of such patients [36, 37]. Moreover, even in anephric patients bone biopsies often show no histologic evidence of osteomalacia [38]. Why such patients fail to develop evidence of vitamin D deficiency is not clear. The persistence of normal or even elevated serum phosphorus levels might protect uremic patients from osteomalacia; this hypothesis is suggested by the finding that the degree of osteomalacia is inversely related to serum phosphorus levels in end-stage renal failure [39].

Reduced skeletal response to PTH. Skeletal resistance to the calcemic action of PTH also contributes to hypocalcemia in patients with renal insufficiency. The calcemic response to a standardized infusion of parathyroid extract is subnormal in patients with moderate to advanced renal insufficiency, and in those undergoing dialysis [40]. Recovery from induced hypocalcemia in patients with creatinine clearances of 35–90 ml/min is delayed as compared to results in normal individuals; this phenomenon occurs despite a greater augmentation in serum iPTH levels in the patients with mild renal insufficiency. These observations indicate that skeletal resistance to PTH appears early in the course of renal insufficiency [6]. Although the mechanisms responsible for the impaired calcemic response to PTH remain uncertain, alterations in vitamin D metabolism have been incriminated [41, 42].

Effect of anticonvulsant drugs. Treatment with phenytoin (Dilantin®) also might contribute to bone disease in the patient we are discussing here. The long-term ingestion of phenytoin, phenobarbital, or both is associated with a high incidence of osteomalacia in nonuremic patients treated for seizure

disorders [43, 44]. Jubiz et al found low serum levels of 25(OH)D but normal levels of $1,25(OH)_2D$ in patients treated with anticonvulsant drugs who had clinical evidence of osteomalacia [45]. Hahn et al have suggested that these drugs might activate a hepatic microsomal P-450 enzyme, and that this activation might lead to abnormal hydroxylation, changing vitamin D and $25(OH)D_3$ to biologically inactive sterols [46]. Pierides et al reported a higher incidence of symptomatic bone disease in dialysis patients treated with barbiturates and phenytoin than in patients not receiving such treatment [47, 48]. Because of the normal serum level of 25(OH)D in our patient, phenytoin treatment probably did not contribute significantly to his bone disease. His serum level of 25(OH)D, however, is lower than that observed in most residents of southern California, where sunlight exposure is usually substantial.

Clinical manifestations of renal osteodystrophy

Now I should like to examine the clinical manifestations in this patient. Bone pain that develops with renal osteodystrophy is often subtle and insidious in onset; the axial skeleton—back, hips, and ribs—is most commonly involved, but pain can involve the knees, heels, and shoulders. Symptoms are often aggravated by sudden changes in position, e.g., when the patient turns over in bed or sits up. Because the pain is related to motion, patients often become sedentary and sometimes even bedridden. Symptoms can be independent of the specific type of skeletal pathology present. Pain might be worse at night, but little relationship exists between the bone pain and temperature or climate. Physical findings usually are absent; consequently, the symptoms commonly are attributed to minor trauma or a psychosomatic cause. The degree of pain does not necessarily correlate with the extent of radiographic abnormalities; thus, patients with severe lesions can be free of symptoms, although it is somewhat unusual for patients to be symptomatic in the absence of radiographic abnormalities. Many other signs and symptoms have been associated with high levels of PTH [Table 2]. Massry and Goldstein recently suggested that PTH might even be a uremic toxin [49].

I believe that the patient's muscle weakness deserves some attention, because this symptom is commonly overlooked despite the fact that myopathy occurring in conjunction with renal osteodystrophy is very common. We recently presented our experience with 7 uremic patients who had severe proximal muscle weakness [50]; all but one had been treated with long-term maintenance dialysis, and the slowly progressive symptoms had existed for an average of 24 months before treatment. Abnormalities of gait were present in all patients; 3 patients exhibited a waddling, "penguin" gait that is characteristic of the proximal myopathy of vitamin D deficiency [51]. Two patients had weakness when they elevated their arms, and they experienced difficulty in combing or setting their hair. Of the 7 patients, 6 had difficulty rising from a chair and were unable to climb stairs. Depite evidence of proximal weakness, distal muscle strength, e.g., strength of the hand grip, frequently was normal. The myopathy is associated with normal serum enzymes, creatinine phosphokinase, and transaminase; electromyographic changes are usually nonspecific.

Because of its slow, insidious nature, the myopathy often is overlooked or attributed to debility in dialysis patients who have other evidence of chronic illness. Although the pathogenesis of proximal myopathy in patients with chronic renal failure remains uncertain, muscle weakness has been attributed to hyperparathyroidism [52], phosphate depletion [53], and abnormal vitamin D metabolism [51, 53]. We and others have observed significant, prompt improvement in muscular weakness during treatment with $1,25(OH)_2D_3$ [27]. Our finding of such muscle weakness in patients who have markedly elevated, normal, or even undetectable levels of serum iPTH suggests that factors other than PTH play a pathogenetic role. We have noted serum calcium levels of 8.1 to 11.3 mg/dl and serum phosphorus levels of 2.9 to 5.5 mg/dl in patients with myopathy. Moreover, myopathy has improved during treatment with $1,25(OH)_2D_3$ even without a change in serum levels of calcium or phosphorus. In 2 patients, muscle strength improved while serum iPTH levels remained unchanged. Moreover, bone biopsies from 5 patients revealed divergent results: we found osteomalacia in 2, marked osteitis fibrosa in one, and "mixed" lesions in 2 others. In one pa-

Table 2. Clinical manifestations of calcium and phosphorus abnormalities in renal failure[a]

Bone pain	Acute periarthritis
Myopathy	Hypertension
Pruritus	Spontaneous tendon rupture
Muscle cramps	Calciphylaxis
Fractures	Neuropathy
Retardation of growth	Altered mentation
Skeletal deformities	Impotence
Pseudogout	Pancytopenia

[a] Adapted from Nortman DF, Coburn JW, *Postgraduate Medicine*, vol 64, no 5, Nov 1978, © McGraw-Hill, Inc.

tient, a muscle biopsy revealed atrophy of type-2 fibers, a finding typical of the myopathy associated with vitamin D deficiency [54]. Electron microscopic examination of muscle biopsies in uremic patients has revealed severe degenerative changes, with disorganization of myofibrils and dispersion of Z-band material; these abnormalities reverted to normal following treatment with $25(OH)D_3$ [55].

Altered muscle contraction and relaxation have been reported in vitamin D-deficient animals [56]. Defective calcium uptake by the sarcoplasmic reticulum in skeletal muscle has been noted with vitamin D deficiency [57] and experimental uremia [58]; moreover, treatment of uremic animals with $1,25(OH)_2D_3$ reversed this abnormality [58]. Altered calcium transport by the sarcoplasmic reticulum of muscle could arise from abnormal vitamin D metabolism. The mechanism whereby $1,25(OH)_2D_3$ affects muscle function is unknown, because specific $1,25(OH)_2D_3$ receptors resembling those found in other target tissues, such as the kidney, intestine, and parathyroid glands, appear to be absent in muscle [59]. Why muscular weakness does not occur more often in uremia is uncertain, since low plasma levels of $1,25(OH)_2D_3$ are common in patients with advanced renal failure [23, 24].

Some additional comments regarding the clinical and biochemical findings in this patient are worthwhile. He had no evidence of skeletal disease when his advanced, chronic renal insufficiency was first identified. Moreover, he developed significant osteitis fibrosa despite reasonable control of serum phosphorus levels. Careful maintenance of normal serum phosphorus levels clearly can reduce the incidence of secondary hyperparathyroidism [60], but significant symptoms still develop in some patients, perhaps because therapy is not initiated until long after parathyroid hyperplasia is well established. The elevation of plasma alkaline phosphatase, which occurs slowly over many weeks or months in patients with bone disease, has not been a useful differentiating factor for the type of bone disease.

Interpreting serum PTH assays

Before proceeding to the issues of diagnosis and management of renal osteodystrophy, a few comments about the determination of serum iPTH are necessary. Many clinically available assays for serum iPTH utilize antisera that primarily detect the carboxyl-terminal fragments of PTH. It now seems certain that the native PTH molecule, a single-chain peptide of 84 amino acids, is quickly cleaved by the liver into amino-terminal and carboxyl-terminal fragments [61, 62]; the carboxyl-terminal fragments are inactive but remain in the circulation with a longer "half-life" than either the 1-84 intact PTH molecule or the biologically active, 1-34 amino-terminal fragment. Moreover, these carboxyl-terminal fragments are not degraded by the liver but rely entirely on the kidney for degradation and clearance from the blood [63]. The plasma half-life of carboxyl-terminal fragments is markedly prolonged when renal function is decreased, and serum iPTH levels, measured with antisera directed toward the carboxyl terminal moiety of the PTH molecule, often are markedly elevated [64, 65]. Serum iPTH in the patient under discussion today was measured in the research laboratory of Dr. Frederick Singer, with the Burroughs Wellcome antiserum 211/32. This antiserum is directed in large part toward the intact PTH molecule. Thus, the serum iPTH level that was fivefold higher than normal is quite significant; such a degree of elevation with an assay utilizing a carboxyl-terminal antiserum might be "normal" for uremia. A good correlation has been reported between serum iPTH levels, measured with a carboxyl-terminal antiserum, and morphometric changes in bone due to secondary hyperparathyroidism [65]; unfortunately, such data are not available for many widely used assays of iPTH. For the appropriate use of serum iPTH measurements, the physician should know the degree of elevation of serum iPTH that occurs in uremic patients simply because of the retention in the circulation of biologically inactive fragments [63]. Ideally, one also should use a PTH immunoassay that correlates with the histomorphometric bone findings of secondary hyperparathyroidism; unfortunately, such data are not currently available.

Diagnosis of renal osteodystrophy

With the observation of high levels of serum iPTH and radiographic findings of subperiosteal resorption in our patient, the bone biopsy finding of osteitis fibrosa is not surprising. Although obtaining a properly undecalcified specimen from a bone biopsy is the most desirable way to diagnose skeletal lesions, appropriate radiographic techniques also can be very useful. The use of fine-grain x-ray film combined with magnification of the x-rays can greatly increase the sensitivity of x-rays in detecting abnormalities and can aid in the follow-up of patients, particularly when the films are viewed by a radiologist with expertise in metabolic bone disease [66, 67]. The use of fine-grain, industrial-quality x-ray film is not popular with radiology departments

because these films cannot be developed automatically; however, film ordinarily used for mammography can be a satisfactory substitute. Meema and his colleagues reported that the use of fine-grain x-ray film and magnification techniques remarkably improves the radiologist's ability to detect osteitis fibrosa [67–69]. In patients with secondary hyperparathyroidism, cortical striations frequently are seen in the shafts of the phalanges and metacarpals, and presumably represent enlarged haversian canals within the bone [67]. The x-ray techniques capable of detecting osteomalacia are far less sensitive; in our experience, pseudofractures or Looser's zones are unusual in uremic patients with osteomalacia [70]. Radiographic signs of rickets can develop in children, but such findings are not helpful after closure of the epiphyses. The x-rays of patients with osteomalacia usually show only demineralization or osteopenia.

Recent data from laboratories in Germany [71], the United Kingdom [72], and this country [37, 73] indicate the existence of distinct subcategories of metabolic bone disease in patients with kidney disease. Moreover, the type of skeletal disease is important in determining the patient's response to treatment with $1,25(OH)_2D_3$ or other active vitamin D sterols. Our work with these subgroups of bone disease was conducted in conjunction with Drs. Donald Sherrard, Arnold Brickman, Frederick Singer, Eugene Wong, and Anthony Norman. We evaluated bone biopsies by quantitative morphometric techniques in approximately 60 highly selected uremic patients who were treated with $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$ [73–77]. Repeat bone biopsies were performed in many patients after 6 to 12 months. These patients, all of whom had advanced renal failure and most of whom were undergoing dialysis, were selected because of the presence of symptomatic bone disease, marked radiographic abnormalities, or both. The patients comprised four distinct categories (Table 3). One group, of which the patient presented today is representative, had osteitis fibrosa with substantial marrow-space fibrosis and increased bone turnover as measured by double tetracycline labeling. Biopsies from this group frequently exhibited an increase in unmineralized osteoid that lay beneath active osteoblasts; such unmineralized osteoid arises because of a lag in mineralization of newly formed matrix rather than because of defective mineralization.

A second group has been termed "mild." The bone biopsies in these patients revealed less than 0.1% of marrow space filled with fibrosis but showed increased resorption surface. These patients characteristically have increased serum iPTH levels. Few patients with symptomatic bone disease have this type of skeletal pathology; most have responded favorably to treatment with $1,25(OH)_2D_3$.

Table 3. Skeletal lesions in 50 patients with severe renal osteodystrophy[a]

	Fraction of surface area		
	Afflicted %	Mineralized %	Fibrosis %
Osteitis fibrosa	39	> 80	> 2.0
Mild	15	> 85	< 0.6
Osteomalacia	33	< 80	< 1.5
Mixed	13	< 80	> 2.0
Normal	—	> 94	0

[a] Modified from Ref. 73.

Bone biopsy in a third subgroup showed osteomalacia with wide osteoid seams (greater than 20% of the bone surface not mineralized); tetracycline labeling revealed a delay in mineralization, with slow bone turnover. Biopsy in the fourth group showed "mixed lesions," with evidence of both osteitis fibrosa and osteomalacia; these patients had evidence of high bone turnover, but the areas of unmineralized osteoid were substantially greater than in patients with osteitis fibrosa alone. Serum iPTH levels measured with the antiserum described above correlated well with marrow fibrosis; strikingly elevated levels of serum iPTH were present only in the patients with osteitis fibrosa or "mixed lesions."

The patients with osteitis fibrosa or pure osteomalacia were separated into two subgroups on the basis of their response to treatment with $1,25(OH)_2D_3$ (Table 4). Patients with osteitis fibrosa, by far the largest subgroup, showed an improvement in symptoms and a decrease in serum iPTH and alkaline phosphatase. Sequential bone biopsies revealed substantial improvement, with reduction in marrow-space fibrosis and improved bone mineralization. The patient under discussion today is representative of this group. A smaller subgroup of patients with biopsy-proved osteitis fibrosa exhibited a rapid increase in serum calcium levels during treatment with $1,25(OH)_2D_3$; this hypercalcemia necessitated withdrawal of therapy. Neither serum levels of iPTH, alkaline phosphatase, nor the extent of bone abnormalities differed in these two subgroups. On the other hand, serum calcium levels exceeded 10.5 to 11.0 mg/dl before initiation of treatment with $1,25(OH)_2D_3$ in the

patients who developed marked hypercalcemia. At subsequent surgery or at autopsy, the latter group of hypercalcemic patients was found to have massive parathyroid hyperplasia. These observations suggest that treatment with $1,25(OH)_2D_3$ might aid in the identification of patients needing parathyroid surgery [78].

The patients with pure osteomalacia also comprised two subgroups, which were determined by the response to treatment with $1,25(OH)_2D_3$. The patients in one subgroup showed no improvement of symptoms during treatment with $1,25(OH)_2D_3$; the serum iPTH levels were normal or undetectable and the bone biopsies disclosed no marrow-space fibrosis or increase in resorptive surface. These patients had a tendency to develop hypercalcemia during treatment with either $1,25(OH)_2D_3$, another form of vitamin D, or even oral supplements of calcium alone. Indeed, the marked propensity for developing hypercalcemia suggested that bone was not significantly contributing to the "buffering" of extracellular calcium [76]. Repeated bone biopsies showed no improvement after prolonged treatment with $1,25(OH)_2D_3$ even though the serum calcium was sustained above normal. Plasma levels of 25(OH)D were either normal or elevated, perhaps because of prior treatment with vitamin D_3. Thus, such patients appear to have defective bone mineralization that is related neither to levels of calcium or phosphorus in the extracellular fluid nor to treatment with vitamin D. These patients often had recurrent rib and hip fractures and back pain, and they experienced progressive debility. Patients from the Newcastle area of the United Kingdom have exhibited a similar clinical picture [79, 80]; their skeletal disease has been attributed to excessive levels of aluminum in the tap water used for the preparation of dialysate [81]. Epidemiologic data from sporadic patients in the United States fail to implicate aluminum in tap water, and the cause of this disease remains obscure [76].

The other subgroup with predominant osteomalacia had pretreatment levels of serum calcium that were generally below 10.5 mg/dl, serum iPTH levels that were slightly above normal, and small areas of marrow fibrosis on bone biopsy. These patients exhibited clinical improvement during treatment with $1,25(OH)_2D_3$, although the bone mineralization recovered only partially following treatment with $1,25(OH)_2D_3$ for 6 to 12 months.

For the entire group of patients treated with $1,25(OH)_2D_3$, the major pretreatment observations that were useful in predicting a favorable response to $1,25(OH)_2D_3$ included a serum calcium level below 10.5 mg/dl and some elevation of serum iPTH levels (Table 4). A similar separation of patients with renal osteodystrophy during treatment with $1\alpha(OH)D_3$ has been reported by investigators in the United Kingdom [80, 82, 83].

Management of renal osteodystrophy

Before discussing the therapeutic use of $1,25(OH)_2D_3$ (Rocaltrol®) in the patient presented today, I should like to comment regarding general principles of managing altered calcium and phosphorus metabolism in uremia. The management objectives for altered divalent ion metabolism should be: *(1)* maintaining the blood levels of calcium and phosphorus as near normal as possible; *(2)* preventing the development of parathyroid hyperplasia

Table 4. Serum biochemical observation before and after treatment with 1,25-dihydroxy-vitamin D_3 in uremic patients

Type of bone disease	No. of patients	Response to Rx	Serum iPTH[e]		Calcium		Phosphorus		Alkaline phosphatase		25(OH)D
			C[a]	T[b]	C	T	C	T	C	T	C
			ng/ml		*mg/dl*		*mg/dl*		*IU/ml*		*ng/ml*
Osteitis	21	R[c]	2.8 ± 0.3	1.0 ± 0.3	9.4 ± 0.2	10.1 ± 0.3	4.5 ± 0.2	5.0 ± 0.3	297 ± 61	139 ± 35	38 ± 4
fibrosa	4	F[d]	3.1 ± 0.4	2.2 ± 0.5	11.1 ± 0.3	17.8 ± 0.9	5.8 ± 0.6	5.7 ± 0.9	173 ± 26	260 ± 109	—
Osteo-	10	F	0.2 ± 0.1	—	10.5 ± 0.2	11.8 ± 0.2	4.7 ± 0.1	5.1 ± 0.2	174 ± 15	219 ± 23	58 ± 10
malacia	6	R	1.5 ± 0.7	0.4 ± 0.1	8.7 ± 1.8	9.8 ± 0.9	5.9 ± 0.6	5.1 ± 0.7	259 ± 133	153 ± 76	31 ± 7
Mild	7	R	1.5 ± 0.3	0.4 ± 0.1	9.8 ± 0.1	10.3 ± 0.3	4.4 ± 0.5	5.0 ± 0.3	121 ± 34	80 ± 22	—
Mixed	8	R	2.1 ± 0.7	0.6 ± 0.2	7.2 ± 0.4	8.8 ± 0.3	4.6 ± 0.3	4.8 ± 0.3	501 ± 153	137 ± 41	25 ± 4

[a] C = control, pre-treatment values.
[b] T = values at end of treatment.
[c] R = responders.
[d] F = treatment-failure group.
[e] Measured with Burroughs Wellcome antisera.
All data are mean ± SE.
Modified from Ref. 77.

or, if secondary hyperparathyroidism is already established, suppressing PTH secretion; *(3)* restoring the skeleton to normal; and *(4)* preventing and/or reversing extraskeletal deposition of calcium. Of these factors, the control of serum phosphorus is probably the most important and can be accomplished by moderately restricting the dietary intake of phosphorus to 0.8 to 1.0 g/day and by administering aluminum hydroxide or aluminum carbonate to bind phosphate in the gut. Because of the variability of phosphorus absorption in patients with uremia, the dosage of aluminum-containing compounds must be adjusted on an individual basis. Serum phosphorus levels should be measured every 2 to 4 weeks to avoid either hyper- or hypophosphatemia, as the latter can predispose to osteomalacia. Dietary calcium intake should be adequate. We currently recommend oral calcium supplements that provide 1.0 gram of calcium per day; calcium is prescribed only when the serum phosphorus level is controlled. The dialysate calcium concentration should be maintained at 6.0 to 6.5 mg/dl (3.0–3.25 mEq/liter) to prevent either the loss or gain of calcium during dialysis.

The indications for the use of vitamin D sterols are only currently being established. These compounds should not be given to patients who have uncontrolled hyperphosphatemia (i.e., serum phosphorus > 6.0 mg/dl). After the serum phosphorus has been controlled, vitamin D sterols are indicated: *(1)* in the presence of hypocalcemia unresponsive to calcium supplementation through diet or dialysis; *(2)* when there is evidence of overt secondary hyperparathyroidism, particularly when the serum calcium is below 11.0 mg/dl; *(3)* for osteomalacia, particularly when it coexists with secondary hyperparathyroidism; *(4)* in children with chronic renal failure [29]; *(5)* when the need exists for concomitant anticonvulsant therapy; and *(6)* in patients who exhibit symptoms of proximal myopathy. It is not yet known whether vitamin D should be used prophylactically in all patients with end-stage renal disease.

Other management considerations include *(1)* the use of appropriate levels of dialysate magnesium (0.5–0.7 mEq/liter) to avoid hypermagnesemia [84]; *(2)* the use of water treatment in preparation of dialysate to remove fluoride and aluminum, and to regulate calcium and magnesium levels; *(3)* avoidance of unnecessary treatment with barbiturates, phenytoin, and comparable drugs; and *(4)* maintenance of normal acid-base status. The specific benefits of some of these measures have not been firmly established, however.

The man described today illustrates several characteristics of patients with severe osteitis fibrosa who respond favorably to treatment with $1,25(OH)_2D_3$. Symptoms usually improve within 1 to 2 months after initiation of treatment [74, 77], although symptomatic improvement can be delayed on occasion [85]. Serum alkaline phosphatase can rise during the first few weeks of treatment and then slowly fall toward normal. The serum calcium level might not increase during the first several weeks or months of treatment, even with doses of $1,25(OH)_2D_3$ as large as 1.0 μg/day; this is particularly true in patients with radiographic evidence of extensive skeletal disease. The serum phosphorus levels, obtained immediately before each dialysis, often decrease significantly during the first month of treatment and slowly increase thereafter. After 8 months of treatment, our patient developed significant hyperphosphatemia despite an increase in the dosage of aluminum hydroxide. It is well recognized that $1,25(OH)_2D_3$ increases intestinal absorption of calcium and phosphorus [26, 86]. Serum calcium and phosphorus might not increase during the initial period of treatment because of substantial remineralization of the skeleton. Later, when serum alkaline phosphatase has decreased, serum calcium and phosphorus levels commonly increase. This patient illustrates a significant relationship between the development of hypercalcemia and a decrease of serum alkaline phosphatase to normal during treatment with $1,25(OH)_2D_3$. A reduction in the dosage of $1,25(OH)_2D_3$ is indicated when the alkaline phosphatase decreases to normal. This patient exhibits another common finding seen during treatment with $1,25(OH)_2D_3$, a prompt fall in the serum levels of both phosphorus and calcium shortly after withdrawal of treatment. A major advantage of $1,25(OH)_2D_3$ over other forms of vitamin D is the short persistence of a biologic effect after the withdrawal of treatment [87, 88]. Thus, this sterol can be used more safely than other forms of vitamin D that act for a longer time after the drug is discontinued [89].

Finally, parathyroidectomy should be reserved for patients with definite evidence of secondary hyperparathyroidism (subperiosteal erosions and significantly increased iPTH levels). Surgery might be indicated in these patients if they also have persistent hypercalcemia, progressive or symptomatic extraskeletal calcification, a persistently elevated

serum calcium x phosphorus product that is recalcitrant to other therapy, or calciphylaxis [90].

Questions and answers

DR. J. P. KASSIRER: Before $1,25(OH)_2D_3$ or $1\alpha(OH)_2D_3$ were available, a number of groups reported that patients who had substantial renal osteodystrophy, particularly osteitis fibrosa, responded effectively to vitamin D_2 or other vitamin D preparations. The problem was that these patients frequently developed sustained hypercalcemia. The question is, what is the course of the hypercalcemia induced by $1,25(OH)_2D_3$? Does it typically respond promptly to reduction or elimination of therapy? Do you sometimes have to treat the hypercalcemia by other means?

DR. COBURN: One of the major advantages of 1,25-dihydroxy-vitamin D over other forms of vitamin D is its relatively short half-life: the circulating half-life is probably 3 to 5 hours, although its biologic effect might be somewhat longer. Nonetheless, when one discontinues the drug, the hypercalcemia usually abates within 2 to 3 days without special treatment. Only rarely are special procedures, such as dialysis with a calcium-free dialysate, needed.

DR. KASSIRER: The response in the patient discussed today is apparently typical of patients who receive $1,25(OH)_2D_3$; not only do their serum calcium levels rise, but their serum phosphorus levels rise as well. Why do you worry about the rise in serum phosphorus levels in these patients? Are you concerned about it only because of the possibility of metastatic calcification or do you have other reasons?

DR. COBURN: The appearance of phosphate retention and hyperphosphatemia causes one to worry, not only because secondary hyperparathyroidism is aggravated but because an elevated calcium x phosphorus product increases the risk of extraskeletal calcification. We have seen no increase in serum iPTH when serum phosphorus is raised during therapy with $1,25(OH)_2D_3$, possibly because the serum calcium is usually slightly higher, and also because of the action of $1,25(OH)_2D_3$ on the parathyroid glands.

DR. J. J. COHEN: You indicated that patients who have predominant osteomalacia histologically do not respond predictably to the administration of vitamin D preparations. Isn't it paradoxical that the one bony change thought to be the specific consequence of vitamin-D deficiency does not respond to hormone replacement as well as the bone disease due to parathyroid excess does?

DR. COBURN: In patients with exclusive osteomalacia and normal or increased plasma levels of 25-hydroxy-D, we have given $1,25(OH)_2D_3$ and raised their serum calcium levels to above normal for weeks or even months in an effort to improve their severe, symptomatic bone disease. We also have allowed serum phosphorus levels to increase in an effort to induce healing. If one increases serum calcium and phosphorus levels in the osteomalacia secondary to vitamin D deficiency, the unmineralized osteoid will calcify. We believe that the failure of healing in the uremic patient represents an abnormality of bone matrix that is unrelated to levels of serum calcium or phosphorus, or to an abnormality affecting vitamin D. Morphologically, this disorder appears the same as one described in England in an area around Newcastle on Tyne. In England the condition has seen blamed on the presence of excess aluminum in the tap water used to prepare dialysate [81, 93]; however, the 18 or 20 dialysis patients we have seen with this disorder come from diverse areas of the country. Because many other patients who have undergone dialysis in the same units have not developed bone disease, I do not think one can justify blaming such sporadic cases on excess aluminum in the water supply. In a preliminary study, we have measured bone aluminum in several of these patients and in dialysis patients with other types of bone disease. The bone aluminum levels were above normal in all, but they were higher in the patients with this mineralizing defect than in patients with other types of bone disease [94]. Serum iPTH levels also were lower than in other uremic patients. Thus, the accumulation of aluminum or other trace elements in bone, and the low levels of serum iPTH might contribute to defective mineralization. The source of aluminum is uncertain but might be related to ingestion of phosphate-binding antacids in the sporadically occurring cases. Such patients might have increased intestinal permeability to aluminum or an abnormality of bone matrix leading to aluminum accumulation; obviously, these comments are speculative.

DR. COHEN: What you are calling osteomalacia, therefore, should not be interpreted as being related specifically to vitamin D deficiency.

DR. COBURN: That is correct. Osteomalacia is a descriptive term used to indicate defective mineralization of bone, no matter what the cause.

DR. BORIS SENIOR *(Chief, Division of Pediatric Endocrinology, NEMCH)*: Two questions: Is a decreased response to $1,25(OH)_2D_3$ ever caused by poor calcium absorption from the gut in patients with renal failure? Do uremic patients generate less calcium-binding protein in response to 1,25-dihydroxycholecalciferol?

DR. COBURN: In an extensive study, we examined the relationship between the dose of $1,25(OH)_2D_3$ and the change in intestinal calcium absorption during the oral administration of $1,25(OH)_2D_3$ in patients with chronic renal failure and in normal individuals [86]. We could stimulate calcium absorption just as readily in the uremic patients as in normals. Also, the patients with osteomalacia who do not improve readily become hypercalcemic when they are given small doses; thus, we conclude that their intestines are responding to $1,25(OH)_2D_3$. It should be noted that we are giving a hormone by mouth that is normally produced in the kidney and then enters the blood stream. It is possible that the intestinal cells might "see" the hormone first in larger amounts than might occur if the drug were administered intravenously. Perhaps the effect of $1,25(OH)_2D_3$ should be evaluated using another route of administration.

Blood levels of $1,25(OH)_2D_3$ have been measured only recently and only in occasional patients. One child, with typical osteitis fibrosa, responded sluggishly and had blood levels of $1,25(OH)_2D_3$ that were lower than might be expected, suggesting poor absorption of the sterol. This problem obviously needs to be explored further.

DR. MARCK MOLITCH *(Division of Endocrinology, NEMCH)*: Some patients with modest renal insufficiency have had an acceleration of renal failure when treated with $1,25(OH)_2D_3$. I would like to hear your comments on this observation.

DR. COBURN: One report from Denmark [95] indicates that patients with creatinine clearances of 15–40 ml/min who received $1,25(OH)_2D_3$ experienced small but reversible increases in serum creatinine compared to a "placebo" group given only a very small dose of vitamin D. I wonder whether the augmented absorption of phosphorus or calcium that is stimulated by $1,25(OH)_2D_3$ might worsen renal function. Animal experiments [96] and clinical studies by Walser and colleagues [97] suggest that glomerular filtration rate might improve in renal failure during phosphate depletion. These trials of $1,25(OH)_2D_3$ should be repeated with careful attention to phosphate homeostasis; the researchers should ensure that phosphate retention does not occur.

DR. SENIOR: Some have suggested that any adverse effect of 1,25-dihydroxycholecalciferol on renal function results from hypercalcemia. Do you agree?

DR. COBURN: Certainly hypercalcemia could worsen renal function. However, the animal experiments that I cited indicate that renal failure progresses in a subtotally nephrectomized rat fed a regular diet. When the diet is depleted of phosphate, renal function improves. The serum calcium levels usually are higher in the phosphate-depleted rat than in the rat fed a normal diet. Thus, the change in renal function could arise from either calcium or phosphate retention.

DR. MOLITCH: I am intrigued by the subgroup of uremic patients who have normal calcium levels and normal or low PTH levels. What is the explanation for these findings?

DR. COBURN: That is a very interesting question. The regulatory mechanisms that control serum calcium and calcium balance in these patients are not understood. Several patients have exhibited a tendency to become hypercalcemic with oral calcium loads, very small doses of either vitamin D_2 or $1,25(OH)_2D_3$, or exposure to high calcium-containing dialysates. Without the presence of functioning kidneys to excrete calcium, such patients have lost one mechanism for regulating serum calcium; the bone behaves as though it does not participate in the "buffering" of extracellular fluid calcium. Thus, these patients seem to have a very small miscible calcium pool and can develop protracted hypercalcemia when any calcium is administered because they have no means of excreting calcium. Why this should occur, I do not know. It would be well to test calcium kinetics to resolve the question of the pool size; this study has not been done because such patients are seen only sporadically and because regular dialysis would complicate such an evaluation.

Six or seven of our patients with these findings had undergone parathyroidectomy for preexisting well-documented osteitis fibrosa. In these patients, hyperparathyroid bone disease might have been converted to the less common disorder, osteomalacia. The tendency toward normal or even slightly increased serum calcium levels might be responsible for preventing hyperparathyroidism in the others; we are beginning to evaluate the parathyroid response to acute hypocalcemia in these patients. Thus, a primary failure of the parathyroid glands

could exist, and the low levels of serum iPTH could contribute to the decreased bone turnover.

DR. SERAFINO GARELLA (*Chief, Division of Renal Diseases, Rhode Island Hospital, Providence, Rhode Island*): Do you use bone densitometry in diagnosing renal osteodystrophy?

DR. COBURN: Bone densitometry only tells you the amount of bone mineral and provides no information about its cause. A low value can occur with osteoporosis, osteomalacia, or other bone disorders. I think bone densitometry is a useful adjunct in monitoring a patient's course of therapy, but it should be used with other studies such as careful bone x-rays to help explain the qualitative aspects of bone changes.

DR. GARELLA: Except for its duration of action, the activity of dihydrotachysterol appears similar to that of 1,25-dihydroxy-vitamin D in treating some of these conditions. Do you know of another major difference?

DR. COBURN: Dihydrotachysterol (DHT) is a non-natural sterol, discovered somewhat by accident in the laboratory. Because physiologists and biochemists are less interested in this quirk of the laboratory than in natural sterols, we know far less about the action of DHT on bone than we do about the more recently identified, naturally occurring sterols. Dihydrotachysterol must be 25-hydroxylated before it acts, and the dose required for action is larger than that needed for $25(OH)D_3$, and almost as high as that for vitamin D_2 itself. The action of DHT can be ineffective in patients with liver disease or those taking anticonvulsant medications. Also, there seems to be more variability in the doses needed to produce a given effect than is the case for $1,25(OH)_2D_3$. We have found beneficial effects of $1,25(OH)_2D_3$ in several patients who allegedly had received DHT in doses as large as 2 mg/day. However, a carefully controlled comparison of the effects of DHT and $1,25(OH)_2D_3$ has not been performed.

DR. GARELLA: Do you have any suggestions regarding the treatment of patients who suffer primarily from osteomalacia?

DR. COBURN: I wish I did. The results of various therapeutic maneuvers have been equivocal or negative in most patients. We have tried reducing the ingestion of aluminum hydroxide to ensure that there is no phosphate depletion. In some we have replaced the acetate in the dialysis bath with bicarbonate; in others we have tried lowering dialysate magnesium so that hypermagnesemia does not exist; and in some, we have initiated special treatment of tap water to reduce trace metals. There was no apparent benefit from any of these treatment modalities. The patients with osteomalacia often are bedridden, and some have actually died because of deformities of the chest or spine produced by their bone disease. We have given some of these patients $1,25(OH)_2D_3$, and a few have exhibited decreased pain, improved muscle strength, and a decrease in serum alkaline phosphatase to normal. Improvement as shown by bone biopsy was negligible, however. The patients who had a clinical response to $1,25(OH)_2D_3$ tolerated larger daily doses before developing hypercalcemia than did those who failed to respond [94].

We currently are evaluating another naturally occurring vitamin D sterol—24,25-dihydroxy-vitamin D_3 [98]; this sterol is believed by some to stimulate bone formation, although others believe it is merely a degradation product of vitamin D. Preliminary results with $24,25(OH)_2D_3$ in a few patients show a decrease in serum calcium and a greater tolerance for $1,25(OH)_2D_3$ or DHT without causing hypercalcemia. Most such patients given $24,25(OH)_2D_3$ with either $1,25(OH)_2D_3$ or DHT have shown chemical, biochemical, and histologic improvement [99].

We have little idea about the pathogenesis of this type of osteomalacia. It might represent several different diseases; for example, cadmium excess might be a cause in one patient, aluminum excess in another, and deficiency of $24,25(OH)_2D_3$ in yet another. Obviously, I am speculating.

DR. MARTIN GELMAN (*Renal Division, St. Elizabeth's Hospital, Boston, Mass.*): Slatopolsky has had some success treating osteomalacia using 25-hydroxy-vitamin D_3. Have you had a similar experience?

DR. COBURN: In a multi-center trial with 25-hydroxy-vitamin D_3, the patients were separated into those who responded well—usually patients with secondary hyperparathyroidism—and those who didn't. Patients with osteomalacia who were treated with 25-hydroxy-vitamin D_3 failed to respond. The observation that serum levels of 25(OH)-vitamin D_3 were normal or high in our patients led us away from a therapeutic trial with this sterol.

DR. DONALD HRICIK (*Renal Fellow, NEMCH*): Should we be using "phosphate binders" and dietary phosphate restriction in patients with progressive renal disease before overt hyperphosphatemia develops?

DR. COBURN: You can marshall strong arguments for doing so; Slatopolsky, Bricker, and colleagues have presented convincing evidence that you

should [2–5]. This program can reduce serum iPTH levels, but long-term studies have not evaluated its safety. In countries in which people eat diets lower in phosphate than those consumed in the U.S., a high incidence of osteomalacia has been reported. Thus, one might be trading secondary hyperparathyroidism for another type of bone disease. Studies are needed to evaluate this question.

DR. NICOLAOS E. MADIAS (*Renal Service, NEMCH*): Are there any data on the levels of $1,25(OH)_2$-vitamin D in human acute renal failure?

DR. COBURN: None of which I am aware.

DR. ROBERT RUBIN (*Chief of Nephrology, Lemuel Shattuck Hospital, Boston*): Your comments regarding treatment for uremic myopathy are interesting. Do you have any quantitative data in patients whom you have treated with $1,25(OH)_2D_3$?

DR. COBURN: The data I presented are based on a clinical, retrospective analysis of patients who were identified because of symptoms thought to arise from bone disease. We now are carrying out a double-blind prospective study in dialysis patients, using clinical tests of muscle strength as an index of myopathy, but we do not yet have data available. I mentioned our experience because most physicians are not aware of the myopathy and its potential reversibility.

DR. COHEN: Would you summarize what you regard as the indications for parathyroidectomy in patients with end-stage renal disease?

DR. COBURN: Yes. Several syndromes can be improved with parathyroid surgery. Before parathyroidectomy is considered, secondary hyperparathyroidism must be verified by either *(1)* a bone biopsy showing osteitis fibrosa, *(2)* an x-ray showing subperiostal absorption, or *(3)* markedly elevated serum iPTH levels, measured with an assay that correlates well with bone disease. When one of these criteria is met, surgery may be considered under several situations. When a uremic patient develops spontaneous hypercalcemia, I would consider parathyroidectomy. If a patient with documented secondary hyperparathyroidism rapidly develops symptomatic bone disease, for example, serious fractures, I would proceed to parathyroid surgery. On occasion, patients have developed calciphylaxis with progressive ischemic necrosis of the fingertips, toes, and elsewhere [99]. This syndrome occurs in dialysis patients or in renal transplant recipients with normal renal function. The disease often progresses rapidly, and patients can die as a consequence: given the observation that some of these patients improve dramatically following parathyroid surgery, surgery should be performed with haste. One also should consider parathyroidectomy in uremic patients with extensive soft tissue calcification when the hyperphosphatemia has been totally resistant to attempts to deplete phosphate stores. Serum phosphorus usually decreases transiently after surgery; then one must convince these patients to follow rigorous measures for phosphate restriction. Persistent hypercalcemia after successful renal transplantation might be another indication for surgery, particularly if renal function is deteriorating.

DR. COHEN: When you do recommend parathyroidectomy, do you suggest that the surgeon perform autotransplantation of the gland?

DR. COBURN: Total parathyroidectomy with autotransplantation of parathyroid tissue into the forearm has been recommended to avoid the need for subsequent neck exploration if hyperparathyroidism recurs, and to have the parathyroid tissue in a more accessible place should removal of more parathyroid tissue be necessary. Our parathyroid surgeon prefers not to perform the additional surgery; he rapidly freezes and stores the parathyroid tissue for subcutaneous implantation should evidence of persistent hypoparathyroidism appear. The internist or nephrologist involved should work closely with an experienced parathyroid surgeon to determine the best procedures to follow in patients who undergo parathyroid surgery.

DR. KASSIRER: With new hormonal insights into the pathogenesis of divalent cation and anion disturbances in uremia, do you have new insights into *tertiary* hyperparathyroidism?

DR. COBURN: This is a term that I prefer not to use because most data indicate that in most patients with uremia, serum iPTH levels will decrease when the blood calcium level is raised; thus, there is no evidence for autonomy of parathyroid function. One study has shown that one can produce persistent hypercalcemia in rats by transplanting the parathyroid gland from 40 normal rats into the subcutaneous tissues [100]. Hypercalcemia does not necessarily indicate that there is something different about parathyroid cell function. Research in cows has shown that basal PTH secretion persists even during marked hypercalcemia [101]. Thus, increased iPTH levels might exist in uremic patients with mild hypercalcemia on the basis of marked parathyroid hyperplasia. It would seem better to reserve the term "tertiary" hyperparathyroidism for patients who develop parathyroid adenomas, a rare occurrence.

DR. J. T. HARRINGTON: Much has been written about parathyroid hormone as a uremic toxin. What are your thoughts about this notion?

DR. COBURN: Data have been reported that suggest that PTH is a pathogenetic factor responsible for a number of clinical manifestations of uremia. Increased calcium content of several soft tissues, including skin, blood vessels, and brain, has been reported to be associated with marked secondary hyperparathyroidism. The accumulation of calcium in the brain might be a factor leading to an abnormal electroencephalogram, particularly in acute uremia; an increase in calcium content of peripheral nerves has been reported but there is disagreement. I already mentioned the occurrence of soft tissue necrosis or calciphylaxis; hyperlipidemia has been attributed in part to high levels of PTH; and anemia has been associated with secondary hyperparathyroidism. Whether the anemia is caused by a toxic effect of PTH, to marrow fibrosis from osteitis fibrosa, or to some other factor is uncertain. There are anecdotal experiences of an increase in libido and reversal of impotence following a decrease in PTH levels. However, controlled studies have not been done. It has been thought that the abnormal carbohydrate metabolism present in uremia might be related to high PTH levels. The evidence supporting the role of PTH in these conditions has only recently begun to accumulate, and this is an area that we will view with interest.

DR. COHEN: Is there a role for measuring ionized calcium as opposed to total calcium levels in patients with renal failure?

DR. COBURN: Unfortunately, few data are available. With the development of effective, specific ion electrodes for measuring calcium, some laboratories can now measure the ionized calcium readily. Uremia is a condition that can be associated with an increase in the complexed fraction of calcium, so there might be a decrease in ionized calcium level for any level of total blood calcium. Further investigation is needed to pursue this question.

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